The pathological mechanisms of β-amyloid in the brain of Alzheimer's Disease and controls

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Research question and background

We are investigating the mechanisms of different forms of Aβ in the brain and CSF in Alzheimer´s Disease (AD). We have been focusing our investigations on which different forms of Aβ exist in the AD brain and their influence on different pathological pathways. These studies are important and might have an important impact for the development of future therapeutic strategies for AD.

Methods and tissues used

We have studied how Aβ affects histones and its relationship to the expression of candidate genes as well as its resulting proteins, such as BDNF and reelin in the 6 obtained AD patients and 6 control subjects. In addition we have studied the presence of choline acetyltransferase (ChAT) in the brain and CSF in relation to its contracting enzymes, acetylcholinesterase and butyrylcholinesterase and their ability to form BABA-complexes by performing several ELISA-based assays. We have also studied which Aβ forms that are present in the brain by setting up a completely new method to measure Aβ oligomers as well as the characterizing the ApoE genotype, protein and mRNA levels. We have also characterized the Omi-protein (also known as HtrA2) and its gene expression by western blot and RT-PCR.

Results and conclusion

In AD post-mortem brain, we have found a strong association between soluble Aβ and histone H3 homeostasis. We have also found that Aβ forms complexes together with BuChE and AcHE which can enhance the progression of the disease. In AD, the protein levels of BDNF are reduced in the superior parietal gyrus compared to non-demented controls while the reelin protein levels are increased. We also found that soluble ChAT in the CSF originates from the brain and there is also evidence for differential pattern of ChAT activation in AD brains compared to control. The epigenetic data has been presented at scientific conferences, such as AD/PD 2013 in Florence, Italy, the Neuroscience meeting 2013 in San Diego, USA, the AAIC Conference 2014 in Copenhagen and in the Keystone symposia conference in Neuroepigenetics 2015 in Santa Fe, USA.

We are now in the end of analysing all data and have so far generated enough material for 3 papers that will be submitted in the autumn of 2015. Further characterization of Aβ levels using MS will be done during the spring and we are planning to perform further studies on which genes that are influenced by the epigenetic modifications found.

Finally, we would like to express our sincere gratitude and appreciation of the excellent work performed at NBB and the involved clinics. It makes it possible for us to perform our research and hopefully provide new diagnostics and ultimately treatment strategies for this devastating disease.